REMARKS/ARGUMENTS

Claims 1-3 and 5-13 are pending in this application. Claims 14-43 have been withdrawn without prejudice due to the Examiner's previous restriction requirement. Claim 4 has been canceled. These claims have been withdrawn or canceled without prejudice to, or disclaimer of, the subject matter thereof. Applicant reserves the right to file divisional and/or continuing applications directed to the subject matter of any claim withdrawn or canceled for any reason.

I. Claim Rejections Under 35 U.S.C. §102(b)

Claims 1-3, 5 and 13 have been rejected under 35 U.S.C. §102(b) as being anticipated by Patterson *et al.* (IDS, WO 01/00198; "the Patterson *et al.* reference"). Office Action mailed December 01, 2005 ("OA"), page 2. As Applicant will explain more fully below, this rejection is improper because the Patterson *et al.* reference does not constitute prior art under §102 of the Patent Act.

In order for a reference to qualify as prior art under 35 U.S.C. §102, the reference must enable the claims of the patent application it is cited against. *In re Donahue*, 226 USPQ 619, 621 (Fed. Cir. 1985); *In re Sasse*, 629 F.2d 675, 681 (CCPA 1980); *In re Borst*, 345 F.2d 851, 855 (CCPA 1965), *cert. denied*, 382 U.S. 973 (1966). We are confident that, upon further review of this issue, the Examiner will agree that the Patterson *et al.* reference does not enable the teachings or claims of the present application as amended, and thus cannot serve as the basis of a 35 U.S.C. §102(b) rejection.

The test for enablement is whether the disclosure of a reference would allow one of ordinary skill in the art to make and use the claimed invention without undue experimentation. *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916); *In re Wands*, 8 USPQ.2d 1400, 1404 (Fed. Cir. 1988); MPEP § 2164.01. Factors to be considered in this analysis include (1) the quantity of experimentation necessary to reach the claimed invention from the disclosure of the cited reference, (2) the amount of direction or

guidance presented in the reference for reaching the claimed invention, (3) the presence or absence of working examples in the cited reference, (4) the nature of the claimed invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims. *In re Wands*, 8 USPQ.2d at 1404; *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986).

An analysis of these factors shows that the Patterson *et al.* reference does not enable the claims of the present application as amended and thus cannot be cited as prior art under 35 U.S.C. §102.

A. Quantity of Experimentation Needed to Reach the Claimed Invention

The present application teaches and claims a method of treating cancer by increasing the delivery of chemotherapeutic agents to a tumor by using an endothelin B agonist to selectively increase blood supply to the tumor. The Patterson *et al.* reference describes treating cancer through the use of endothelin *antagonists* which *decrease* blood flow to tumors. Further, the Patterson *et al.* reference teaches that endothelin B agonists "enhance proliferation and/or delay differentiation" (Patterson *et al.*, page 7, lines 13-15)) and should be used as an experimental control when testing the beneficial effects of endothelin antagonists (see, for example, page 26, lines 22-29; page 28, lines 17-19). Because the Patterson *et al.* reference does not include any beneficial uses of endothelin B agonists in the treatment of cancers, a great deal of experimentation remained following the publication of this reference to reach the claimed invention. As such, this factor supports the conclusion that the Patterson *et al.* reference does not enable the claims of the present application and thus cannot be cited as prior art under 35 U.S.C. §102(b).

B. Amount of Direction or Guidance Presented in the Cited Reference for Reaching the Claimed Invention

As stated, the Patterson *et al.* reference does not disclose a beneficial use of endothelin B agonists in the treatment of cancer. Thus, this reference provides no

direction or guidance for reaching the claimed invention. While the Patterson *et al.* reference does describe using ILR1620 in the treatment of cancer, this reference mischaracterizes IRL1620 as an endothelin antagonist. Because endothelin antagonists restrict blood flow to tumors, the Patterson *et al.* reference does not provide any indication that IRL1620 could be used as an endothelin agonist to increase blood flow to a tumor to selectively increase the delivery of chemotherapeutic agents. As a result, this factor also supports the conclusion that the Patterson *et al.* reference does not enable the claims of the present application as amended and thus cannot be cited as prior art under 35 U.S.C. §102(b).

C. Presence or Absence of Working Examples in the Cited Reference

There are no working examples in the Patterson *et al.* reference that disclose the use of endothelin agonists, and more particularly IRL1620, as agents that can be used to increase blood flow to tumors to selectively increase the delivery of chemotherapeutic agents. Thus, this factor also supports the conclusion that the Patterson *et al.* reference does not enable the claims of the present application and cannot be cited as prior art under 35 U.S.C. §102(b).

D. Nature of the Claimed Invention, State of the Prior Art, Relative Skill of Those in the Art and Predictability or Unpredictability of the Art

As these factors are inter-related, they are addressed in combination.

While cancer researchers are, as a group, highly-skilled, the art of developing safe and efficacious treatment protocols is exceedingly challenging and unpredictable. Therapies that should work based on "known" mechanisms often fail or create unforeseen side effects that negate their beneficial uses as a treatment. As a result of this unpredictability in the art, theories and proposed mechanisms must be tested before commenting on their validity and potential efficacy.

The presently-claimed invention describes a novel mechanism to enhance the effectiveness of chemotherapeutic agents. The effectiveness of these

chemotherapeutic agents is enhanced by selectively increasing their delivery to tumors rather than other non-cancerous parts of the body as seen with more conventionally-used global or systemic administration protocols. Due to the nature of the claimed invention, the state of the prior art, the relative skill of those in the art, and the unpredictability of this art, a reference disclosing a method of treating cancer by restricting blood flow to tumors through using endothelin antagonists should not be read to enable the wholly-different claimed invention of using endothelin agonists to increase blood supply to a tumor to selectively increase the delivery of chemotherapeutic agents. As a result, these factors also support the conclusion that the Patterson *et al.* reference does not enable the claims of the present application and thus cannot be cited as prior art under 35 U.S.C. §102(b).

E. Breadth of the Claims

The claims of the present application, as amended, are not described or taught by the Patterson *et al.* reference. Further, these claims are not unduly broad in light of the teachings of the present application. The present application provides data showing that IRL1620 provides an effective mechanism to increase blood supply to tumors, thus providing a mechanism to selectively enhance the delivery of chemotherapeutic agents to the tumor.

Because the Patterson *et al.* reference does not enable the claims of the present invention as amended, it is not prior art under 35 U.S.C. § 102. Thus, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1-3, 5 and 13 under 35 U.S.C. § 102(b).

II. Claim Rejections Under 35 U.S.C. §103(a)

A. 35 U.S.C. §103(a) Claim Rejections Over Patterson *et al.* in Combination with Rowinsky *et al.*

The Examiner next rejected claims 1-3, 5-6 and 13 under 35 U.S.C. §103(a) as being unpatentable over Patterson *et al.* (IDS, WO 01/00198, 2001; "the Patterson *et al.*

reference") in combination with Rowinsky *et al.* (N. Engl. J. Med. 1995; 332: 1004-1014; "the Rowinsky *et al.* reference"). OA, page 4. The Examiner alleges that such a rejection is proper because the Patterson *et al.* reference "teaches ... a method of treating a solid tumor comprising administering to a human in need thereof a therapeutically effective amount of IRL1620 and a therapeutically effective amount of a chemotherapeutic agent" while Rowinsky *et al.* "discloses ... paclitaxel and its importance as a chemotherapeutic agent." *Id.* There are several reasons why these rejections are not proper. While it is true that the Patterson *et al.* reference discloses the use of IRL1620 as a cancer treatment that can be used in combination with another chemotherapeutic agent (page 8, line 20; page 23, lines 17-19), this disclosure is based solely on the incorrect characterization of IRL1620 as an endothelin antagonist, when in fact, IRL1620 is an endothelin B *agonist*. Further, inherency is not a proper argument to raise against a new method or discovered mechanism of action under 35 U.S.C. §103(a) because what is "inherent is not necessarily known" and "obviousness cannot be predicated on what is unknown." See, for example, *In re Rijckaert*, 28 USPQ2d 1955, 1955 (Fed. Cir. 1993) citing *In re Spormann*, 150 USPQ 449, 452 (CCPA 1966) and *In re Newell*, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989).

1. Because IRL1620 is now known to be an endothelin *agonist*, the Patterson *et al.* reference teaches away from the presently-claimed invention.

Reduced blood supply is thought to inhibit tumor growth and/or survival. Thus, the Patterson *et al.* reference describes the use of endothelin antagonists to decrease blood supply to a tumor as a treatment for cancer. The Patterson *et al.* reference further (incorrectly) describes IRL1620 as an appropriate endothelin antagonist to use in accordance with its teachings. As stated earlier, endothelin agonists in the Patterson *et al.* reference are described as compounds that "enhance proliferation and/or delay differentiation" (Patterson *et al.*, page 7, lines 13-15)) and are compounds that should be used as experimental controls when testing the beneficial effects of endothelin antagonists (see, for example, page 26, lines 22-29; page 28, lines 17-19). Because IRL1620 is now known to be an endothelin agonist, what Patterson *et al.* now teaches

to one of ordinary skill in the art is that ILR1620 "enhance[s] proliferation and/or delay[s] differentiation" (Patterson *et al.*, page 7, lines 13-15) and that this compound could be used to block the beneficial effects of endothelin antagonists in the treatment of cancer. Thus, upon reviewing the Patterson *et al.* reference, one of ordinary skill in the art would conclude that IRL1620 should not be used in the treatment of cancer, and indeed, could stimulate tumor growth and survival. Because the Patterson *et al.* reference teaches away from the presently-claimed invention as amended in this manner, it should not serve as the basis of a 35 U.S.C. §103(a) rejection.

2. The Patterson *et al.* reference describes IRL1620 as a stand-alone treatment whereas the present application describes IRL1620 as an adjuvant to a treatment.

Even if the Patterson *et al.* reference did teach one of ordinary skill in the art the use of IRL1620 as a cancer treatment in combination with another chemotherapeutic agent, this teaching still would be fundamentally different than that taught and claimed by the present application. The Patterson *et al.* reference describes the use of endothelin antagonists as cancer treatments in and of themselves. The endothelin antagonists inhibit the growth and/or survival of a tumor by restricting blood flow to the tumor. The Patterson *et al.* reference then states that the endothelin antagonists could be administered "in conjunction with other compositions for treatment." page 23, lines 17-18. The Patterson *et al.* reference does not, however, describe how another composition would interact with the endothelin antagonist treatment it describes. Thus, the Patterson *et al.* reference simply describes the use of two independent treatments in combination with the apparent rationale of producing an additive or synergistic effect. This type of combination therapy is quite different from that described and claimed in the present application.

In the present application, there is no claim that an endothelin B agonist would, by itself, provide a beneficial effect in the treatment of cancer. Instead, the present application uses IRL1620 as an adjuvant to increase the efficacy (and reduce unwanted side effects) of chemotherapeutic agents by enhancing the delivery of chosen

chemotherapeutic agents to a tumor through the selective increase of blood flow to the tumor. The present application does not teach the sole use of IRL1620 as a cancer treatment as (erroneously) characterized in the Patterson *et al.* reference, but instead teaches the use of IRL1620 as an adjuvant to be administered *only* in combination with another chemotherapeutic agent. Because of this fundamental difference and the fact that what is not known cannot be obvious, the present rejections under 35 U.S.C. §103(a) are not proper and Applicant respectfully requests that the Examiner reconsider and withdraw these rejections.

B. 35 U.S.C. §103(a) Claim Rejections Over Patterson *et al.*

The Examiner next rejected claims 1-3, 5 and 7-13 under 35 U.S.C. §103(a) as unpatentable over the Patterson *et al.* reference (IDS, WO 01/00198, 2001). OA, page 6. According to the Examiner, Patterson *et al.* "teaches ... a method of treating a solid tumor comprising administering ... a therapeutically effective amount of IRL1620 in conjunction with [a] therapeutically effective amount of a chemotherapeutic agent." *Id.* As described *supra*, and for the same reasons, a §103(a) rejection based on this rationale is not proper. Thus, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1-3 and 5.

The Examiner rejected claims 7-13 because while "Patterson *et al.* does not teach that the endothelin B agonist and chemotherapeutic agent are administered simultaneously, as a single composition, as a separate composition or sequentially [or] wherein the chemotherapeutic agent is administered prior to or after the endothelin B agonist", such practices would have been prima facie obvious to one of ordinary skill in the art." OA, page 7. Because claims 7-13 depend from claim 1 as amended, which Applicant believes is now in condition for allowance, Applicant also requests that the Examiner reconsider and withdraw the rejection of claims 7-13.

allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited.

If there are any further fees due in connection with the filing of the present reply, please charge the fees to undersigned's Deposit Account No. 50-3207. If a fee is required for an extension of time not accounted for, such an extension is requested and the fee should be charged to undersigned's deposit account.

Respectfully submitted,

Dated: 1/17/06

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